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Original Articles

Reaction of metformin with dicarbonyl compounds. possible implication in the inhibition of advanced glycation end product formation

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Abstract

Dicarbonyl compounds such as methylglyoxal and glyoxal are extremely reactive glycating agents involved in the formation of advanced glycation end products (AGEs), which in turn are associated with diabetic vascular complications. Guanidino compounds such as aminoguanidine appear to inhibit AGE formation by reacting with α-dicarbonyl compounds. The aim of this work was to study whether the antihyperglycemic agent metformin (a guanidine-like compound) might react with reactive α-dicarbonyls. Metformin was incubated at pH 7.4 and 37° in the presence of either methylglyoxal or glyoxal and reaction products analysed by HPLC coupled to mass tandem spectrometry. AGE formation on albumin by methylglyoxal and glyoxal in the presence or absence of metformin was also studied by measuring the fluorescence at 370/440 nm after albumin–AGE isolation by ultrafiltration. As a standard for mass spectra analysis, a metformin–methylglyoxal adduct was chemically synthesised and characterised as a triazepinone (2-amino-4-(dimethylamino)-7-methyl-5,7-dihydro-6*H*-[1,3,5]triazepin-6-one). The results obtained showed that metformin strongly reacted with methylglyoxal and glyoxal, forming original guanidine–dicarbonyl adducts. Reaction kinetic studies as well as mass fragmentation spectra of the reaction products were compatible with the presence of triazepinone derivatives. In the presence of metformin, AGE-related fluorescence after albumin incubation with either glyoxal or methylglyoxal was

decreased by 37% and 45%, respectively. These results suggest that besides its known antihyperglycemic effect, metformin could also decrease AGE formation by reacting with α-dicarbonyl compounds. This is relevant to a potential clinical use of metformin in the prevention of diabetic complications by inhibition of carbonyl stress.

Author Keywords: advanced glycation end products; carbonyl stress; dicarbonyl compounds; glycoxidation; metformin; triazepin

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